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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,432	THWAITES, ERIC	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/463,939.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 08/22/2008. Claims 18-36 have been canceled. New claims 37-51 are pending and have been examined on the merits.

Information Disclosure Statement

Applicant has submitted a proper 1449 on 11/16/2007 which has been considered by the Examiner. Additional references that were listed for consideration under the title of "Additional Information" on the information disclosure statement (namely US 3,711,462 and EP 1522579) have also been considered.

Response to Arguments

Applicant's arguments filed 08/22/2008 with respect to claims 37-51 have been fully considered but are moot in view of the new ground(s) of rejection below. The arguments have been addressed in so far as they relate to the new grounds of rejections. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that Capiau et al do not teach or suggest a method of producing a glycosaminoglycan, which is not a cell-bound protein of a bacterial agent. Applicant

asserts that Capiau et al do not teach or suggest the adjustment of the pH of the fermentation broth following the addition of calcium chloride as claimed by Applicant.

This is not found persuasive because Laustsen et al teach that a microfiltration process using calcium chloride as a flocculating agent can be used with any fermentation-derived product of interest (page 1 para 18). Capiau et al teach that the pH is adjusted either before or after the addition of the flocculating agent (column 4 lines 40-45).

Applicant argues that addition of calcium chloride followed by pH adjustment results in a high yield of glycosaminoglycan. Applicant asserts that the glycosaminoglycan is more stable at the conditions used in Applicant's process.

This is not found persuasive because both Capiau et al (column 4 lines 37-40) and Laustsen et al (page 3 para 48) teach that the pH adjustment of a fermentation broth is a matter of routine optimization and experimentation with the result effective variables being product yield and stability.

Applicant argues that Laustsen et al do not teach or suggest a method of producing a glycosaminoglycan. Applicant argues that Laustsen et al do not teach or suggest the addition of calcium chloride to the fermentation broth followed by an adjustment of the pH of the fermentation broth.

This is not found persuasive because Laustsen et al does teach a microfiltration process using calcium chloride as a flocculating agent that can be used with any fermentation-derived product of interest (page 1 para 18). Capiau et al teach that the pH

is adjusted either before or after the addition of the flocculating agent (column 4 lines 40-45).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 37-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigel et al (WO 99/23227) in view of Kanani et al (US 3,878,093) and Laustsen et al (US 2002/0020668).

Claim 37 is drawn to a method of producing a glycosaminoglycans, comprising a) fermenting a *Bacillus* cell to produce a fermentation broth comprising a glycosaminoglycans; b) adding calcium chloride to the fermentation broth at a concentration of 0.5-3.5 g of calcium chloride per gram of dry mass of the *Bacillus* cell in order to flocculate the *Bacillus* cell; c) after addition of calcium chloride, adjusting the pH of the broth to between 6.5 and 8.5; d) after step c, removing the Bacillus cell and/or high molecular weight contaminants; and e) after step d, recovering the glycosaminoglycan.

Dependent claims include the concentration of the divalent salt (claims 38-40), wherein the *Bacillus* cell is *Bacillus subtilis* (claim 41), wherein the glycosaminoglycan is hyaluronic acid (claim 42), the molecular weight of the glycosaminoglycan (claim 43), removal of the Bacillus cell by filtration (claim 44), diluting the fermentation broth with water (claims 45-47), heating the fermentation broth (claim 48), adding one or more other flocculating agents to the broth (claim 49), adding activated carbon to the broth (claim 50) and purifying the glycosaminoglycan after step e (claim 51).

Weigel et al teach a method of fermenting a microorganism. This microorganism is capable of producing a glycosaminoglycan and secreting it into its medium. In particular it is advantageous, after the glycosaminoglycan has been produced, to sequester the microorganism from its fermentation broth, by a method of flocculating the

microorganism (see p. 63, lines 6-23, for example). In particular the microorganism that produces the glycosaminoglycan can be either a eukaryote or a prokaryote (see p. 58, line 27 to p. 59, line 8, for example; see p. 59, line 18 to p. 60, line 8, for example). In particular, the use of *Bacillus subtilis* is a preferred embodiment of a cultured organism for producing the glycosaminoglycan hyaluronic acid (see p. 59, lines 9-17, for example). These hyaluronic acid molecules span a range of sizes, but fall within the range recited in the instant claim 43 (see p. 79, lines 11-23, for example; see Fig. 9, for example). Filtering and purifying the hyaluronic acid is also taught (page 59, lines 10-26).

Weigel et al do not expressly teach addition of calcium chloride as a flocculating agent.

Weigel et al do not expressly teach adjusting the fermentation broth pH.

Weigel et al do not expressly teach heating the fermentation broth to between 30 and 60 °C.

Weigel et al do not expressly teach diluting the fermentation broth or adding activated charcoal to the fermentation broth.

Capiau et al teach a method of extracting a cell-bound protein of bacterial origin, useful in acellular vaccines, comprising contacting a suspension of the cell-bound protein with a flocculating agent prior to heat treatment (abstract). The combination of a flocculating agent and the heat treatment enhances the yield of protein released fro the cells after a single extraction step and also obviates the requirement for subsequent centrifugation to remove cellular debris (column 2 lines 23-28). An additional advantage

is the elimination of most of the high molecular weight endotoxins which are present in the broth after fermentation (column 2 lines 28-33). A wide range of flocculating agents well known in the art may be employed in the process to improve the handling qualities of the cell suspension following heat treatment. Preferred flocculating agents are materials embodying divalent cations such as calcium chloride (column 3 lines 17-25). The flocculating agent is suitably brought into contact with a suspension of cells under controlled-pH conditions and the liquid volume is adjusted by addition of appropriate buffer (column 3 lines 26-29). The optimum pH for any chosen flocculating agent may be selected by routine experimentation and the pH of the supernatant is suitably adjusted to between 4 and 10, preferably between pH 8.5 and 9.5, **either before or after** addition of an aqueous solution of a calcium salt (column 4 lines 37-45). The slurry of flocculated cells is subjected to a heat treatment of approximately 60 degrees C (column 4 lines 64-65).

Laustsen et al teach a microfiltration process of a fermentation-derived product comprising adding activated carbon to a solution of the product prior to or during the microfiltration process at a temperature from 25 degrees C to 65 degrees C (abstract). The activated carbon and elevated temperature increase process capacity when microfiltering a fermentation-derived product (page 1 para 9). The method may be applied to an untreated fermentation broth or to a fermentation broth that has first been subjected to a pH adjustment, a temperature adjustment, a water dilution and flocculation (page 3 para 43). The optimal pH is normally a compromise between the pH at which the fermentation-derived product of interest is most stable and the pH at which

the solubility of the fermentation-derived product is greatest (page 3 para 48). The microfiltration process is further improved if in addition to the carbon treatments a Ca-product is added prior to or during the microfiltration process. Any soluble Ca compound or any mixture thereof may be used, in particular calcium chloride (page 3 para 52-53). Dilution with 100% water is also taught as desirable (page 4 para 71). Preferred bacteria include *Bacillus* (page 2 para 37).

A person of ordinary skill in the art at the time the invention was made would have been motivated to add divalent salt (such as calcium chloride), change the pH of the fermentation broth, add activated carbon, dilute the fermentation broth and heat the fermentation broth in the method of Weigel et al because Capiau et al and Laustsen et al teach that there are advantages to adding these techniques that allow for the easy purification of fermentation-derived products (such as hyaluronic acid). A person of ordinary skill in the art would have been motivated to optimize result effective parameters (such as the pH, temperature, timing of addition of flocculating agents and pH controlling agents, amount of flocculating agents and dilution of the fermentation broth) in order to enhance the purity of the desired product as well as the ease of collection. A person of ordinary skill in the art would have had a reasonable expectation of success because Weigel et al, Capiau et al and Laustsen et al are all drawn to enhancing the production of purified fermentation-derived products.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the flocculation and filtering methods of Capiau et al and/or Laustsen et al, as well as optimizing the result effective parameters

(such as pH, temperatures and concentration amounts) in a method of producing and purifying hyaluronic acid as taught by Weigel et al.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LS

/Leon B Lankford/

Primary Examiner, Art Unit 1651